August 14, 2000

Reo Menning
Deputy Director
Silicones Environmental, Health and Safety Council
11921 Freedom Drive Suite 550
Reston, VA 20190

Dear Ms. Menning:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Aminosilanes, CAS# 919-30-2 and CAS# 1760-24-3, submitted April 7, 2000. I commend the Silicones Environmental Health and Safety Council for their commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will adequately characterize each SIDS endpoint. On its Chemical RTK HPV Challenge Program website EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the attached Comments on the Chemical RTK web site within the next few days. As noted in the comments, we ask that SEHSC advise the Agency, within 60 days of the posting on the Chemical RTK website, how it intends to pursue its activities on these chemicals. Please respond either by email (oppt.ncic@epa.gov, hpv.crtk@epa.gov, or chem.rtk@epa.gov;) or by regular mail to:

Carol Browner, Administrator
US Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22116
Attention: Chemical Right-to-Know Program

EPA will post your response on the Chemical RTK website.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-260-3470. Submit general questions about the HPV Challenge Program through the Chemical RTK web site comment button or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@.epa.gov.

I thank you for your submissions and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Oscar Hernandez, Director
Risk Assessment Division

Attachment

cc: W. Sanders
C. Auer
N. Patel
A. Abramson

EPA Comments on Chemical RTK Challenge Submission: Aminosilanes

SUMMARY OF EPA COMMENTS

The sponsor, the Silicones Environmental, Health and Safety Council, submitted a Test Plan, Category Justification, and Robust Summaries to EPA and posted a Work Plan (the Tracking System version of Test Plan) on the HPV Tracking System website. EPA posted the submission on the ChemRTK website on April 21, 2000. The proposed information-gathering plan is for two chemicals, 3-(triethoxysilyl)-1-propanamine (CAS No. 919-30-2) and N-[3-(trimethoxysilyl)propyl]-1,2-ethanediamine (CAS No. 1760-24-3), considered by the sponsor to constitute an aminosilanes category.

EPA has reviewed this submission and found that, in general, the test plan and robust summaries were well-organized and easy to follow. However, the Agency reached the following conclusions:

(1) The Test Plan fails to support the proposed information gathering on these two chemicals as part of a category. The submission does not support the proposed analogy between the two substances, either on the basis of chemical structure or existing data. (EPA does accept the comparison of mutagenicity data as a special case; see detailed comments.)

(2) The ecotoxicity robust summaries contain insufficient information to permit an assessment of data adequacy, in part because of special chemical properties that create a need for more details. Proper evaluation of the summaries will depend on the results of the planned hydrolysis tests and submission of additional information, if available, about the existing studies, including test substance preparation and administration. EPA will therefore defer judgement on the adequacy of the available aquatic toxicity data until the hydrolysis data become available.

(3) Transport/distribution estimates may be needed for the trisilanol hydrolysis products of the two chemicals. Although EPA agrees with the sponsor's conclusion that transport/distribution estimates are not meaningful for the parent compounds (CAS Nos. 919-30-2 and 1760-24-3) because of the expected rapid hydrolysis, such calculations may be appropriate for the trisilanol hydrolysis products.

(4) The proposed hydrolysis studies will provide important information that: (a) will aid in the interpretation of the environmental effects and transport/distribution endpoints; and (b) might support an analog-type approach for the two aminosilanes for environmental effects.

(5) It is important to note that these chemicals present special challenges owing to their ready reactivity with water. This affects the measurement and interpretation of their environmental fate and their toxicity. EPA suggests that in such situations, sponsors who identify the known or probable structure of decomposition and degradation products can help EPA and other reviewers to better evaluate and interpret the available data. Some specific examples are indicated in the more detailed comments that follow.

(6) As a general matter, EPA prefers to apply the term "category" to groups of three or more chemicals. Such groups provide a range of endpoint data for similar chemicals that may allow one to identify trends and then use those trends to estimate missing data. On the other hand, extrapolation of data from one of a pair of chemicals to the other, or analog assessment, requires a close and well-supported (not merely hypothetical) relationship between the two chemicals for each endpoint in question. For more on these topics see "Guidance for Development of Chemical Categories in the HPV Challenge Program" and "The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program", at www.epa.gov/opptintr/chemrtk/guidocs.htm.

In order to resolve the issues raised in items 1-3 above, the Agency suggests:

For Item 1: Provide a stronger basis for the proposed extrapolations, or develop individual test plans for the two chemicals.

For Item 2: Perform the planned hydrolysis tests and submit additional information, if available, about the existing studies (see detailed comments).

For Item 3: Perform transport/distribution calculations for the trisilanol hydrolysis products, or provide information showing that those products are unstable even at high dilution.

EPA is requesting that the Sponsor advise the Agency within 60 days how it intends to pursue activities on the chemicals in its submission.

EPA COMMENTS ON AMINOSILANES CHALLENGE SUBMISSION

EPA's comments are organized as follows: General; Category Definition; Category Justification; Test Plan; Specific Comments on Robust Summaries.

General

EPA contacted the sponsor to clarify one apparent contradiction in the Category Justification. Under "Correlation of Environmental Fate", the sponsor stated that "The hydrolysis rate of CAS No. 1760-24-3 has been measured" as $t_{1/2}$ = 24.2 minutes at 25 EC. However, the test plan indicates that both chemicals will be tested for this endpoint. The sponsor explained that they considered the available data to be unreliable, but had neglected to state this in the discussion.

Category Definition

There are some errors in this section (pp. 3-4 of Category Justification). "The aminosilanes...have three carbon atoms linked to a silicon (Si) molecule with an alkoxy group (an alkoxysilane) at one end, **and an amine group or groups at the other end of the three carbon chain**..." and "These materials each **contain three carbon atoms, one with a single amine and the other with two amines.**" This reads as if both substances have only three non-alkoxy carbons, which is clearly wrong for the methoxy compound. Again, in Figure 4 of the test plan, if y = 2, the result is not N-[3-(trimethoxysilyl)propyl]ethylenediamine but rather a smaller diaminopropyl derivative.

An accurate generalized structure for these two chemicals would be $(XO)_3SiCH_2CH_2CH_2NHR$, where R = H, X = ethyl, or R = $CH_2CH_2NH_2$, X = methyl.

Category Justification

The submission presents a case for considering two aminoalkoxysilanes as closely related and for extrapolating data from one to the other. EPA believes the presentation does not adequately support this proposal. The structures appear too different and the available data too sparse to justify an extrapolation approach.

The chemicals are similar in that they both contain reactive alkoxysilane groups and amino groups attached through an alkyl chain. They differ in the type of alkoxy group present (methoxysilane vs. ethoxysilane), the presence of two amino groups in N-[3-(trimethoxysilyl)propyl]-1,2-ethanediamine but only one in 3-(triethoxysilyl)-1-propanamine, and the aminoalkyl chain structure and length.

The submission does not address the possibility that the different alkoxy groups may hydrolyze at different rates in biological systems, leading to different effects. In addition, the silanol portions of the hydrolysis products are not simple homologs (i.e., different by one carbon), but are substantially different in that one compound has a single amino group while the other has an additional aminoethyl group. This

three-atom difference could cause a significant change in the physicochemical properties of the moiety and thus in toxicological behavior. It would have been useful to explore any available data for these two silanol compounds or other ways to compare the $SiCH_2CH_2CH_2NHR$ moieties to support the extrapolation approach for the parent compounds.

It would be helpful to have sample structural formulas showing how the "highly reactive" (p. 4) trisilanol hydrolysis products react further.

The ecotoxicity data as currently reported cannot be evaluated for adequacy (see below), so it is difficult to compare the results for the purpose of an extrapolation approach argument. As the sponsor considered the data to be adequate, they did not address extrapolation issues for ecotoxicity.

The proposed approach is most relevant and important to the sponsor for the health endpoints, where the submitter proposes testing for repeat-dose and reproductive toxicity on one compound (3-(triethoxysilyl)-1-propanamine) and extrapolating those results to the other compound. Available data indicate that for acute toxicity these two chemicals are not toxicologically similar. In both the oral and dermal acute toxicity studies of 3-(triethoxysilyl)-1-propanamine, the kidney is a target organ and severe irritation was observed in the dermal study. On the other hand, no target organ was identified in either the oral or dermal acute toxicity studies of N-[3-(trimethoxysilyl)propyl]-1,2-ethanediamine and there was no irritation observed in the dermal study. The mutagenicity results with both chemicals did show similar (negative) responses. This clearly shows the difficulty of a generic extrapolation approach across all endpoints.

EPA believes the test sponsors needed to address weaknesses in their case such as the apparent difference in target organ mentioned above in order to identify areas where they needed to strengthen their approach. In addition, it might be useful to compare mono- and diamine carbon analogs to determine the possible similarities or differences in toxicity between the two. As presented, on the basis of available information it is difficult to extend the results of testing from one of these substances to the other.

Test Plan

As stated above, EPA believes that the sponsor has not demonstrated the validity of the extrapolation approach for these aminosilanes. Consequently, the proposed plan to test the ethoxy compound for repeat dose/reproductive effects and extrapolate the results to the methoxy compound may not be appropriate without clarification of the "category" issue. Information that might help clarify the latter would be: (a) evidence that the rates of siloxane hydrolysis (at a physiologically relevant pH) for the two compounds are similar; and (b) evidence that at least carbon analogs of the monoamine and diamine are toxicologically similar.

The submitter states that data on transport/distribution are not available and are not appropriate for either material because of their rapid hydrolysis. However, because the hydrolysis products appear not to be readily biodegradable, EPA considers that estimates on transport/distribution of the products should be provided.

Finally, EPA agrees with the sponsor's plan to conduct hydrolysis tests on both test substances. According to the HPV Tracking System (hpvchallenge.com), the sponsor plans to follow OECD Test Guideline 111. EPA suggests the following amendments/modifications to the protocol: (1) because both substances are reported to be hydrolytically unstable, the procedure described on pp. 7-8 of the protocol is expected to be followed. EPA suggests that the sponsor also perform the optional hydrolysis test at pH 1.2 as described on p. 8 of the protocol (to assess hydrolysis in the context of health effects tests); (2) because of the reported potential for polymerization and cross-linking of hydrolysis products in water (see below under comment on the biodegradation robust summaries), EPA suggests that the sponsor analyze the hydrolysis products to determine the extent to which crosslinking or polymerization occur.

Specific Comments on the Robust Summaries

Chemistry

The sponsor's treatment of Melting Point, Boiling Point, Vapor Pressure, Water Solubility, and Partition Coefficient (Log Kow) is sufficient.

Fate

The sponsor's Robust Summary treatment of Hydrolysis and Photodegradation is sufficient.

Biodegradation

The submitter classified these chemicals as "not readily biodegradable." The biodegradability of the substances was determined using a DOC Die-Away Test. EPA notes that the test results are more precisely a measure of the biodegradability of the hydrolysis products than of the parent chemical. In practical terms these processes can't be separated and the results are due to both processes.

The rapid loss of DOC between days 0 and 7 followed by little or no additional biodegradation on days 14-28 is consistent with the rapid hydrolysis of the parent compound followed by rapid biodegradation of the alkanol hydrolysis products. The aminoalkyl trisilanol hydrolysis product may not be degraded under the conditions of the test. If it were, DOC loss would have increased more significantly after day 7.

These results are adequate for assessing the ready biodegradability of the parent compounds. However, there is a potential concern for the silanol hydrolysis products, which can be assumed from the test data to be not readily biodegradable. EPA questions the submitter's unqualified statement that the silanol hydrolysis products form cross-linked products in water (more information about this reaction might have been helpful). At some point the solution of silanol products may become too dilute for the molecules to react rapidly with one another. Yet, in principle, these aminosilanols could still exert ecotoxicity.

Transport/Distribution

The submitter states that data on transport/distribution are not available and not considered appropriate for either material, because they hydrolyze rapidly. However, because the aminoalkyltrisilanol hydrolysis products appear not to be readily biodegradable, estimates of transport/distribution of the products should be provided.

Health Effects

The robust summaries submitted for acute toxicity (oral and dermal for both aminosilanes), mutagenicity (*in vitro* studies with both aminosilanes and an *in vivo* study with 919-30-2), and developmental toxicity (919-30-2) were all considered adequate summaries for the purposes of the U.S. HPV Challenge Program. EPA notes the following:

> Acute toxicity (1760-24-3) Two studies were submitted, both with rats using oral (gavage) administration and dermal administration. LD50 values denote low toxicity (oral, approximately 2.4 g/kg; dermal, > 2 g/kg [no deaths at highest tested dose]).
>
> Acute toxicity (919-30-2) Two studies were submitted, one with rats using oral (gavage) administration and one with rabbits using dermal administration. LD50 values denote low toxicity (oral, between 1.5 and 2.8 g/kg; dermal, 4.3 g/kg). In both studies, the kidney was identified as a target organ. The dermal study noted severe irritation (including necrosis, desquamation and fissuring).
>
> Acute toxicity (general): The two aminosilanes show very different effects (systemic effects to kidney from two different routes of exposure: 919-30-2 only; and severe dermal irritation: 919-30-

2 only), although lethality was similar.

Repeat dose toxicity (no data submitted). An EPA TSCATS search revealed a number of studies with 919-30-2 that might be important: a 9-dose dermal toxicity study in rabbits (9 dosing days is in the "gray area" of acute vs. repeat dose - reference is EPA OTS 89-910000115); and many 8(e) and FYI submissions noting the severe irritation/corrosive nature of this material. Importantly, the nine-day rabbit study did not produce any effects on the kidney (highest dose tested was 84 mg/kg for nine days and 126 mg/kg for three days; the latter dose was stopped due to severe dermal irritation). Although dermal irritation is not a SIDS endpoint, it is worth noting here because of the severity of the effect and the lack of such an effect with the other substance (1760-24-3).

Mutagenicity data. The *Salmonella* assays for both chemicals were properly summarized, and the micronucleus study with 919-30-2 is properly summarized. The data for 1760-24-3, both in the single robust summary (*Salmonella* assay) and in the cited supporting data cover the endpoints of gene mutation and DNA effects (sister chromatid exchanges, or SCEs), but not the endpoint of chromosome mutations. However, EPA agrees with the sponsor that the chromosome mutation data from 919-30-2 are reasonably expected to apply to 1760-24-3, not solely because of the data available on these two chemicals but because EPA's experience with a range of aminosilanes and alkylsilanes confirms the general lack of mutagenicity of these compounds.

Developmental toxicity (919-30-2). Additional information that should be included, if available: (1) in the 'Method' section under Method/Guideline followed, the TSCA test guideline number; (2) in the 'Method' or 'Remarks Field for Test Conditions' sections, information on any dose-range finding studies that provided the basis for selection of the doses used in the full study; and (3) in the 'Results' section, an explanation as to why there were fewer pregnant animals in the treated groups compared with the control group (29/30, 25/30, 26/30, 22/30 for the 0, 20, 100, and 600 mg/kg/day dose groups, respectively).

Other comments on the developmental study: under Correlation of Health Effects, on page 6/6 under Category Justification, there is no mention of the existing developmental/reproductive toxicity data.

Environmental Effects

The submission states that these chemicals are difficult to test owing to their physical and chemical properties. Rapid hydrolysis of these chemicals is expected and thus will not allow a test for water solubility. This complicates interpretation of the available ecotoxicity data. The results of the proposed hydrolysis tests will likely provide important information to help interpret the ecotoxicity data.

EPA evaluated each robust summary and determined that there are problems evaluating all six base set aquatic toxicity test robust summaries. EPA assumes that where study information is given as "not documented" or "not reported" it is not in the full report and thus is not available. However, omission of basic parameters, e.g., water hardness, total organic carbon (TOC), pH, dissolved oxygen (DO), test conditions, etc. from some of the robust summaries limited EPA's ability to judge the hazard associated with these chemicals. EPA used its robust summary guidance document as a guide in reviewing these data (www.epa.gov/opptintr/chemrtk/volchall.htm). In addition, the TOC analytical method used in one or more of the studies only measures total carbon and sheds no light on the actual molecular species in solution, which is expected to change over the course of the experiment without significant alteration of the TOC value (except as some volatilization of alcohol hydrolysis products may occur).

CAS# 919-30-2:

Robust summary–fish. The loading technique used (one dose only) was not appropriate because

an LC50 was not attained. Required robust summary information not provided includes pH, background TOC, DO, hardness, temperature, and test conditions such as number of replicates, stock solution preparation, and time from first preparing stock solution to dosing of test organisms.

Robust summary–algae. Information lacking includes background TOC, temperature, and hardness. More description is needed on preparation and administration of chemical.

Robust summary–daphnid. Missing data elements include number of test organisms per concentration, age, diet, temperature, pH, hardness, alkalinity, background TOC, DO, exposure vessel type, size, lighting, and aeration.

CAS# 1760-24-3:

Robust summary–fish. Total hardness and background TOC were not provided. More information on the dosing solutions is needed, including time from solution preparation to addition of organisms. Report stated that the chemical was added directly to exposure vessels, but did not mention 1) if the organisms were in the tank during the addition, and 2) the manner of addition of the chemical. This chemical may need to be added very slowly (e.g., dropwise) to minimize polymerization.

The sponsor provided as supporting information data from another study that indicate similar toxicity to that reported above; however, important data missing from the study (total hardness, background TOC, how test substance was administered) lessen its usefulness in support of the robust summary.

Robust summary–algae. The seven-day algal test submitted follows an old protocol that is no longer used. The information presented may be useful because 4-day data were presented; however, missing parameters needed to determine adequacy of data include pH, hardness, background TOC, and DO; and more description is needed on preparation and dosing of chemical to the algae.

Data from another study with blue-green algae were also provided but had the same problems outlined above, as well as control growth being insufficient for a 7-day test (only an 11-fold increase over seven days).

Robust summary–daphnid. The data missing in the submission to determine the adequacy of this test are: pH; DO; complete dosing description in test; background TOC; analytical measurements; age of test organisms, and sublethal effects.

EPA agrees with the submitter that these chemicals are difficult to test in aquatic systems. Proper testing of such chemicals may follow the Revised Draft Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures (OECD, January 2000 - available on the OECD website at http://www.oecd.org/ehs/test/monos.htm). This formal guidance was not available at the time the data in question were generated. Among the most important considerations is the stability of the test substance; recommended test conditions depend on the hydrolysis half-life value. Information related specifically to the testing of alkoxysilanes also appears under “Alkoxysilanes” in the document “TSCA New Chemicals Program (NCP): Chemical Categories”, available at www.epa.gov/oppt/newchems/chemcat.htm. While the latter guidance was developed for a different purpose, it contains useful technical information.

Thus, in order to evaluate the adequacy of the ecotoxicity data for aminosilanes, it is essential to have reliable stability in water (hydrolysis) data. Determination of this endpoint for both chemicals is part of the sponsor’s test plan. **EPA therefore will defer judgement on the adequacy of the available aquatic toxicity data until the hydrolysis data become available.**

In addition, especially given these chemicals’ reactivity with water, the sponsor should consider whether

any further details relevant to this factor are available in the studies. For example, in the acute fish test for the methoxy compound, it was clearly stated that undiluted test substance was added directly to the exposure vessels. For the other chemical, however, it appears that the sample was prepared in water before initiation of the test, and the sample solution may have existed long enough for significant sample hydrolysis to occur before exposure of the animals (no mortality was reported at 1000mg/L nominal concentration). In the former case, the actual substance tested may have been mostly starting material, while in the latter the tested material may have been mostly hydrolysis products. Any additional details about sample preparation, storage and administration might improve one's ability to judge the data adequacy and interpret the results. This is a case where the unique properties of a chemical argue for more detail in a summary than might otherwise be necessary.

Followup Activity

EPA requests that the Sponsor advise the Agency within 60 days how it intends to pursue activities on the chemicals in its submission.